Detailed Action

Status of Application, Amendments, and/or Claims

The Arguments, submitted 26 March 2008, has been entered. Claims 1-118 and 124 were cancelled previously by Applicant (16 June 2004).

Claims 119-123 are under examination in the Instant Application.

Withdrawn objections and/or Rejections

35 U.S.C. 101, Product-of-Nature

The rejection of Claim 119 under 35 U.S.C. § 101 for non-statutory subject matter is *withdrawn*. As explained in the last Office Action (1 October 2007, p. 15) the claim had read on polyclonal sera that had not been isolated from the human being or animal. Applicants amended the claim to insert the word "isolated" indicating the *hand of man* (26 March 2008).

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 119-123 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 2-15 of the previous Office Action (1 October 2007). Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or

a well established utility for the reasons set forth in the previous Office Action (1 October 2007), one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the examiner no longer asserts that mRNA levels are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Haynes et al., Pennica, et al, Konopka, et al, Godbout, et al, and Li, et al. Therefore, Applicants arguments concerning those references will no longer be addressed. The basis of the maintained rejections is solely that **gene amplification** levels are not predictive of mRNA or polypeptide levels, and that the gene amplification data presented is not a reliable indicator of disease.

At pages 552-554 of the specification, Table 9 and Example 170 show the results of a gene amplification assay in which genomic DNA encoding PRO1153 had a ΔCt value of at least 1.0 for approximately 6% of two types of lung tumors when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 555, first paragraph). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548 it is stated that samples are used if their values are within 1 Ct of the

normal DNA standard. It is further noted that the ΔCt values in Table 9 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.36).

First, there are several problems with the data provided in this example. The art recognizes that lung cells can be aneuploid without the presence of cancer. Specifically, Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12, of record) reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1153 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO1153 is a diagnostic probe for lung cancer unless it is clear that PRO1153 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO1153 antibodies that bind to the disclosed gene product. The Utility of the claimed antibody depends on that of the disclosed PRO polypeptide, and in order for PRO1153 polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1153 mRNA or PRO1153 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels.

Applicants argue (Remarks/Arguments, 26 March 2008, page 4, for example) that the results presented in the instant Specification are enabling for the antibody that binds the polypeptide of SEQ ID NO: 351. They argue that the PRO1153 nucleic acid is a diagnostic marker for lung adenocarcinomas and squamous cell carcinomas, and point to the results of the amplification assay. The assay indicated (Table 9, Specification) showed a 2-fold or greater fluorescence in some samples of lung adenocarcinoma (LT4), but not others (LT1 through LT3, among others).

Applicant's arguments (26 March 2008) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing an increase in DNA copy number- about 2 fold or greater- in some lung tumors, but not others. The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412, of record) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The specification of the instant application does not complement the low (2-fold) PRO1153 gene expression data with any other data that indicates a role in disease. The asserted

utility for the claimed antibodies is based on the assumption that the PRO1153 gene plays a role in disease or is a marker for disease. However, the instant disclosure does not show reliable fluorescence of PRO1153 even within the same experimental group. In addition, the instant Specification does not provide proper statistical analysis such as reproducibility, standard error rates, etc. When viewed with the evidence of record as a whole, there is no correlation between gene amplification and a role of PRO1153 in disease. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicants assert that the Patent Office has failed to meet its initial burden of proof that claims of Utility are not substantial or credible. They contend that the examiner's reasoning is based on a misrepresentation of the scientific data presented in the cited references and application of an improper, heightened legal standard. Applicants state that whether the PRO gene is amplified in few tumor samples or in the vast number of tumor samples is not relevant to its utility as a tumor marker (26 March 2008, page 8).

Applicant's arguments have been fully considered but are not found to be persuasive. The truth or credibility of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1153 gene, polypeptide and claimed antibody are not useful as cancer diagnostic agents.

Applicants indicate that the PRO1153 nucleic acid was amplified in a significant number of lung tumors and showed a large increase in gene copy number, i.e., at least 2-fold amplification. At pages 4 and 5 of the Response, Applicants argue that the amplification of the nucleic acid encoding the disclosed polypeptide is significant for the detection of lung cancer and cite the Declarations under 37 CFR § 1.132. However, no substantially new arguments have been presented. Except for the Goddard declaration, these declarations were previously considered and discussed by the Examiner in the Office Actions of 14 September 2006 and 1 October 2007. However, it is again noted that the PRO1153 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1153 nucleic acid was amplified in about 6% of the cancer samples studied. No mutation or translocation of PRO1153 has been associated with any type of cancer. In addition, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung. For these reasons, it is not clear that the reported amplification is meaningful. In the absence of any of the above information, all that the specification has done is present evidence that the DNA encoding PRO1153 is amplified in some cancer samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Therefore, based on the totality of the evidence, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether

PRO1153 plays a role in disease or can be used as a marker of disease in the two types of lung tumors tested. Thus, the claimed invention does not provide products or services in "currently available form" to the public, and the asserted utility is not substantial.

The fact remains that the instant specification does not disclose whether or not the PRO1153 gene is *reliably* overexpressed in any tumor tissues. Only about 6% of the experimental samples tested positive, even within each tumor type and subtype. For these reasons the skilled artisan must perform further research in order to reasonably confirm overexpression and specificity of positive fluorescence. The requirement for such further research indicates that the asserted utility of PRO1153 as a cancer diagnostic agent is not substantial. Furthermore, the specification does not disclose the expression levels of PRO1153 protein in any tumor samples, such that one can be sure that the claimed antibody can be used as a tumor marker; such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed regarding the usefulness of the PRO1153 antibody in the diagnosis of cancer is not substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not the PRO1153 gene is overexpressed. The determination of such constitutes further experimentation, indicating that the asserted utility is not substantial. Since the disclosed PRO1153 gene and protein lack utility, there would be no reason to use the claimed antibody to detect PRO1153.

Applicants conclude that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptides and

claimed antibodies have utility in the diagnosis of cancer, and, based on such a utility, one of skill in the art would know exactly how to use the claimed antibodies for diagnosis of cancer.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner concedes that the specification teaches how to make the PRO1153 polypeptide as well as antibodies that bind the polypeptide. However, the specification fails to provide a substantial asserted utility for the PRO1153 gene, and thus the specification also fails to enable the PRO1153 polypeptides and claimed antibodies (specifically, the specification fails to teach the skilled artisan how to use the claimed PRO1153 antibodies without undue experimentation). As discussed above, PRO1153 genomic DNA was found to be slightly amplified in only about 6% of types and subtypes of lung cancer samples compared to a normal DNA control. The data were not corrected for aneuploidy, which was known to be common in cancerous *and non-cancerous* lung tissue. Thus, it is not clear from the gene amplification data whether or not PRO1153 genomic DNA actually is amplified in certain lung tumors. In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO1153 is reliably overexpressed in certain lung tumors based on the disclosure regarding gene amplification, *without further experimentation*. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. In view of such and the lack of guidance regarding how a physician might use information regarding PRO1153 overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO1153 as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/
4 June 2008

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